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REVIEW ARTICLE

Stem cells on regenerative and reproductive science in domestic animals

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Abstract

Stem cells are undifferentiated and self-renewable cells that present new possibilities for both regenerative medicine and the understanding of early mammalian development. Adult multipotent stem cells are already widely used worldwide in human and veterinary medicine, and their therapeutic signalling, particularly with respect to immunomodulation, and their trophic properties have been intensively studied. The derivation of embryonic stem cells (ESCs) from domestic species, however, has been challenging, and the poor results do not reflect the successes obtained in mouse and human experiments. More recently, the generation of induced pluripotent stem cells (iPSCs) via the forced expression of specific transcription factors has been demonstrated in domestic species and has introduced new potentials in regenerative medicine and reproductive science based upon the ability of these cells to differentiate into a variety of cells types in vitro. For example, iPSCs have been differentiated into primordial germ-like cells (PGC-like cells, PGCLs) and functional gametes in mice. The possibility of using iPSCs from domestic species for this purpose would contribute significantly to reproductive technologies, offering unprecedented opportunities to restore fertility, to preserve endangered species and to generate transgenic animals for biomedical applications. Therefore, this review aims to provide an updated overview of adult multipotent stem cells and to discuss new possibilities introduced by the generation of iPSCs in domestic animals, highlighting the possibility of generating gametes in vitro via PGCL induction.

Keywords iPSCs · Cellular therapy · Induced reprogramming · Domestic animals

Introduction

Stem cells are widely known for their unique properties of long-term self-renewal and the ability to differentiate into more specialized cell types. They are commonly divided into three types: embryonic stem cells (ESCs), adult multipotent stem cells, including e.g. the well-known mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs). MSC-based therapies are no longer novel in medicine but are still not fully understood. ESCs and iPSCs present the potential for differentiation into cells derived from all three germ lineages and are therefore pluripotent and considered to possess characteristics allowing to achieve further goals in regenerative medicine. Hence, the study of pluripotent cells in domestic animals may improve our understanding of early mammalian development and also present great potential for innumerable applications in regenerative medicine.

Domestic animals have been used as models for biomedical and clinical applications, mostly for the modelling of human diseases. For example, dog and swine models are now known to offer many advantages over rodents because their physiology is more similar to that of humans and because their lifespan is significantly longer than that of rodents, allowing studies on the long-term safety and efficacy of transplanted cells as treatments for injury or disease (Kuzmuk and Schook n.d.; Starkey et al. 2005).

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Dogs, in particular, have provided valuable models for more than thirty years, especially recently with the study and implementation of cell-based therapies (Schneider et al. 2008; Feitosa et al. 2017). They are considered an adequate model for the study of human disorders due to the similarity of innumerable genetic disorders and chronic and degenerative diseases (Hasiwa et al. 2011; van Steenbeek et al. 2016). In addition, they are present in the same environment as man, which makes them susceptible to a series of disorders shared with us such as diabetes, obesity, cancer, allergies and many others (Volk and Theoret 2013).

Although dogs and cats are already important models for human regenerative medicine, these and other species of domestic and wild animals would greatly benefit from the implementation of stem cell technologies for many additional reasons. For example, the efficient production of stem cells from endangered species creates a unique opportunity for species preservation through gamete production, nuclear transfer, embryo complementation or even future novel technologies (Verma and Verma 2014; Verma et al. 2013). Additionally, multipotent stem cells already have a multitude of clinical applications in domestic animals, mainly for horses, dogs and cats suffering from musculoskeletal injuries and chronic diseases (Vidane et al. 2017; Lessa et al. 2012); however, successes in other species including wild animals and in the treatment of several different disorders have also been reported, sometimes even without proper preclinical trials (Fortier and Travis 2011).

Therefore, this review presents concepts and advances in the research on stem cells from and for domestic small animals, focusing on the use of pluripotent cells derived in vitro in reproductive and regenerative medicine (Fig. 1).

Multipotent stem cells: New concepts, same goals

Multipotent stem cells have long been used in regenerative medicine, even before the term "stem cell" became popular. Almost half a century has passed since Friedenstein and colleagues first reported the presence of fibroblastoid cells in adult bone marrow (BM) and their interesting properties. These cells can be flushed out from the haematopoietic environment, are fibroblast-like, adhere to culture dishes, and exhibit a high replicative capacity in vitro with the ability to further differentiate into adipocytes, chondrocytes, osteocytes or haematopoietic stroma (Friedenstein et al. 2009; Friedenstein et al. 1968; Friedenstein et al. 1974; Friedenstein et al. 1970). These cells were later termed "mesenchymal stem cells" (MSCs).

Over the years, these features have proved not to be exclusive to the bone marrow: MSCs can be derived from several, if not all, other organs and tissues (da Silva et al. 2006), including muscle tissue (Jankowski et al. 2002), dental pulp (Tatullo et al. 2015) and transitory tissues such as the placenta (Abumaree et al. 2017).

The exceptional medical interest in MSCs is mostly because they are post-natal self-renewing cells that can be collected from even an adult organism, expanded, characterized in vitro and re-transplanted into the same individual to promote tissue repair after injury without the imminent risk of tumour formation (Cardoso et al. 2017; Ambrosio et al. 2014). Efficient therapies involving the transplant of bone marrow-derived haematopoietic cells in humans have long been in routine use, and the results are unquestionable (Avivi et al. 2002; Miao et al. 2017; Voltarelli et al. 2011). For instance, a Nobel Prize in Medicine and Physiology was awarded to E. Donnall Thomas and Joseph E. Murray in 1990 for their discoveries concerning "organ and cell transplantation in the treatment of human disease": the first demonstrated that intravenously infused bone marrow cells were able to repopulate the bone marrow and produce new blood cells, while the second successfully diminished the severe "graft-versus-host" reaction (GVH) (www.nobelprize.org/nobel_prizes/medicine/laureates/1990/press.html).

MSCs are believed to be reservoirs of cells that contribute to the maintenance and regeneration of the related tissue in vivo. More recently, the presence of MSCs in virtually every vascularized tissue in an organism has been connected to evidence for a perivascular cell niche, herein called pericytes, that are actually multipotent and may be or behave as tissue-specific stem cells in vivo (da Silva et al. 2006; Birbrair et al. 2014). The extent to which MSCs mesenchymal cells are related to pericytes in terms of characterization and functionality has been extensively discussed (de Souza et al. 2016; Caplan 2008; Birbrair and Borges 2017), and much more information remains to be uncovered.

More recent discussion about multipotent cells isolated from different tissues revealed that the therapeutic potential of MSCs is related to their ability to modulate their microenvironment, or niche, rather than to their ability to differentiate into functional new cells. In 2009, Da Silva Meirelles and colleagues reviewed and discussed some important properties of MSCs, including the secretion of growth factors, cytokines and chemokines, that modulates anti-apoptotic, immunomodulatory, angiogenic, anti-scarring, and chemoattractant pathways, thereby leading to a local regenerative environment in vivo (da Silva et al. 2009). Caplan, in 2015, elegantly and concisely presented the previous beliefs (named "The Old", referring to what was believed until now) and the new information now available for discussion (named "The New", referring to new information about multipotent stem cells). Moreover, although the exact relation between pericytes and MSCs is not yet fully unravelled, the mechanisms involved in the regenerative properties of multipotent cells are now clearly related to trophic factors, and thus the proposal of redefining "MSCs" as "medicinal signalling cells" seems appropriate (Caplan 2015).

The use of MSCs in veterinary medicine has grown rapidly. A large number of clinics worldwide already routinely offer

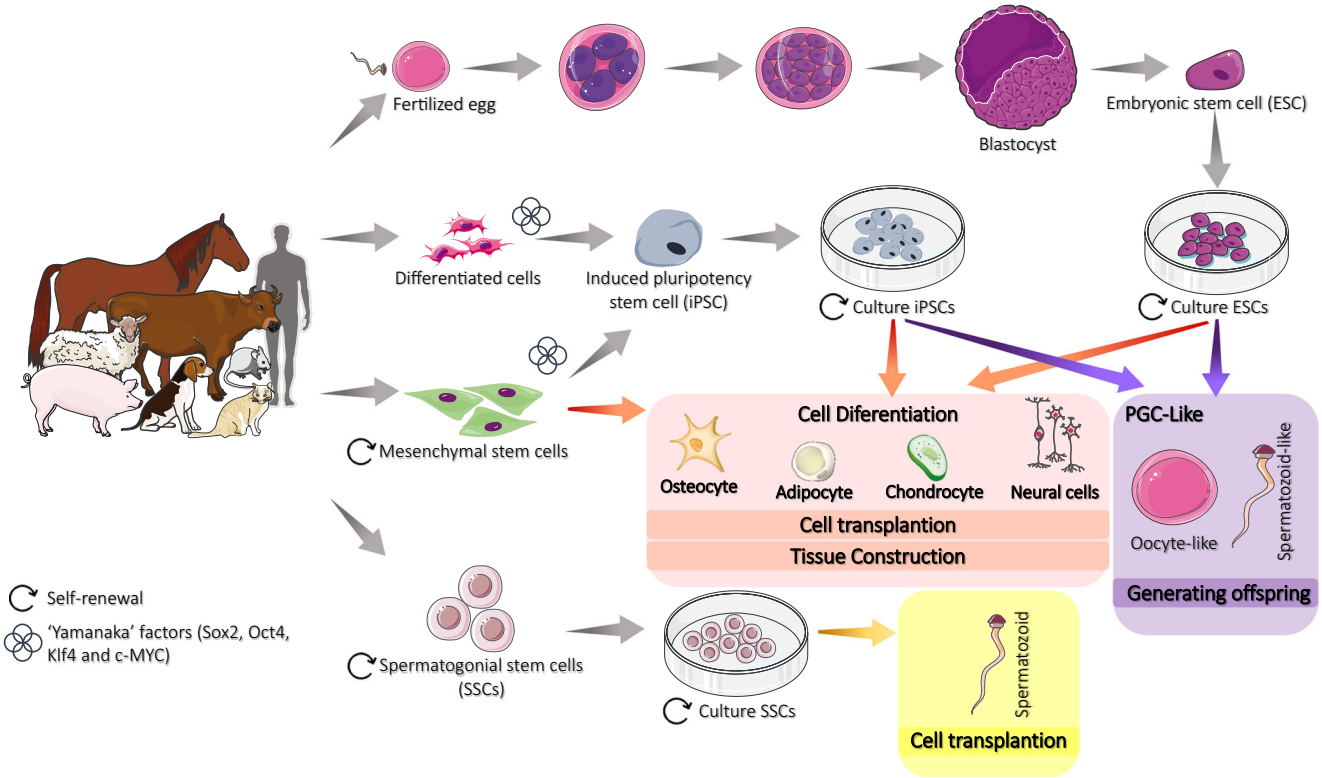

Fig. 1 Schematic model of the possible utilization of embryonic stem cells, induced pluripotency stem cells, mesenchymal stem cells, EnMSCs and spermatogonial stem cells in cell differentiation, cell transplantation, tissue construction and the production of viable gametes

the administration of adult stem cells, even though regimentation and further clinical trials are still needed (Cyranoski 2013). The isolation, culture and characterization of MSCs from different tissues have already been reported in several species, for example, in cats (Cardoso et al. 2017; Ambrosio et al. 2014), dogs (Cardoso et al. 2017; Crovace et al. 2008; Black et al. 2007) cattle and buffalo (Sampaio et al. 2015; Oliveira et al. 2017), horses (Maia et al. 2013; Barberini et al. 2014) and others, and these cells consistently present the same typical characteristics (fibroblastic morphology, mononuclear and adherence to culture) as those in humans or mice.

Although MSCs isolated from bone marrow are the most widely studied for application in regenerative veterinary medicine, the adipose tissue-derived MSCs (AD-MSCs) in the stromal vascular fraction have essentially the same properties as stem cells derived from bone marrow (Kim et al. 2011; Cherubino et al. 2011) with the advantage of greater accessibility and abundance than other types of adult stem cells. Studies in dogs, humans, mice and cattle have demonstrated that AD-MSCs are capable of self-renewal when maintained in culture and can differentiate into other types of cells such as adipocytes, osteocytes, chondrocytes, myogenic and neuronal cells (Russell et al. 2016; Ohsaki et al. 2007; Neupane et al. 2008). Furthermore, Fang et al. (2017) reported evidence of the differentiation of canine AD-MSCs into germ-like cells via the modulation of TGF-B signalling, an important step toward a better understanding of germline specification and to the use of MSCs in the reproductive sciences in domestic animals (Fang et al. 2017).

Particularly in reproductive biology, recent findings have highlighted interesting contributions of a particular cell population in the endometrium, the endometrial stem cells (EnMSCs), in tissue remodeling and engineering. It is known that the uterus undergoes extensive proliferative changes and remodeling in adult mammals throughout the reproductive cycle, and therefore, it is expected that these cells display particular characteristics regarding plasticity and immunomodulating effects (Ghobadi et al. 2015; Verdi et al. 2014).

Cell-based therapies using EnMSCs are promising, and some in vitro or in vivo preclinical and clinical studies including pelvic organ prolapse, heart disorders, ischemic conditions, endometriosis and colitis, for example, are already ongoing (Ulrich et al. 2013; O DF et al. 2017; Xu et al. 2018; Emmerson and Gargett 2016). First described in human and mouse (reviewed in Gargett et al., 2007 and 2015) (Gargett et al. 2007; Gargett et al. 2015), these cells are now characterized is several species including rat (Zhao et al. 2015), cattle (Cabezas et al. 2014; Lara et al. 2017), equine (Cabezas et al. 2018; Rink et al. 2018), sheep (Kurukuti et al. 2006; Ghobadi et al. 2018), swine (Subbarao et al. 2018), and canine (De Cesaris et al. 2017), however no data in domestic felines are reported yet. Elective ovary-salpingo-hysterectomies, particularly in dogs and cats, may provide a cost-effective and, in terms, non-invasive source of adult stem cells. Undoubtedly, a

better characterization of these cells in animals will provide new insights on cellular-based therapies, specially focusing on reproductive disorders.

Although the use of AD-MSCs, EnMSCs or MSCs in general presents great possibilities in regenerative and translational medicine since hurdles related to ethical issues and rejection after transplants are absent, further well-designed, blinded and randomized clinical trials, as well as basic translational research and regulation in veterinary medicine are needed before a full exploitation of their potentials can be realized.

Pluripotent stem cells: The promise and hurdles of embryonic stem cells in domestic animals

Early embryonic development is a highly dynamic period during which paternal and maternal genetic material are epigenetically reprogrammed to constitute and functionally express the recombined unique embryonic genome (Mann and Bartolomei 2002). This reprogramming consists of erasing epigenetic marks, of which DNA methylation is a major component, with exception of the imprinted genes, which are very important to early foetal and placental development (Bressan et al. 2009), along with chromatin conformation alterations modulated by chromatin-modifying agents (CMAs), e.g., histone acetyltransferases (HATs) and histone deacetylases (HDACs). This erasure is followed by the re-acquisition of new epigenetic markers leading to new gene expression patterns that will orchestrate development and cell lineage differentiation (Reik et al. 2001).

In the early cleavage stage embryo, the cells (or blastomeres) are considered totipotent since they retain the potential to develop into embryonic or extra-embryonic tissues. Concurrent with epigenetic reprogramming, minor genome activation of the embryo genome occurs during the first cleavages, and then, an important major activation (embryo genome activation, EGA) occurs at a species-specific moment: at 2 cells in mouse, 4 cells in pigs, 8 cells in cattle and dogs and 8–16 cells in horses and sheep (Hyttel et al. 2010; Meirelles et al. 2004).

After EGA, usually at the morula stage, differential gene expression between cells located in the inner and outer layers can be detected and will lead to, at the blastocyst stage, two morphologically distinct cell populations within the embryo: a cluster of cells within the embryo called the inner cell mass (ICM), which are OCT4 positive, and the trophectoderm (TE) consisting of flat cells, surrounding the ICM and the blastocyst cavity, connected by tight junctions and desmosomes, which are positive for CDX2 and may or may not, in a species-dependent manner, also be positive for OCT4 (Berg et al. 2011).

The TE gives rise to extra-embryonic tissues, while the ICM, classified as pluripotent cells, gives rise to the embryo proper and to the foetal components of the placenta by first differentiating into the hypoblast and epiblast. The latter will subsequently differentiate further during gastrulation into the endoderm, mesoderm, ectoderm, which will give rise to all somatic cell lineages in an organism, as well as into the primordial germ cells (PGCs), which "escape" somatic differentiation signalling by migrating outside the embryo in order to maintain the pluripotency needed to generate functional gametes (Hyttel et al. 2010; McLaren and Southee 1997).

Pluripotent cells, therefore, occur in a temporary state during early development, but the isolation and maintenance of these cells under in vitro conditions has led to the establishment of ESCs capable of self-renewal and differentiation into all three embryonic germ layers.

ESCs were first derived from murine ICM (mESCs). These ESCs form colonies that appear piled or dome-shaped rather than flat and can be propagated in medium containing leukaemia inhibitory factor (LIF) (Evans and Kaufman 1981). These cells were able to colonize the ICM of other mouse embryos after blastocoel injection and form chimeric embryos, frequently contributing to their germ cells (Nichols and Smith 2009). When injected in vivo, they form teratomas, which are benign tumours presenting derivatives of all three germ lines (Nelakanti et al. 2015).

In humans, the isolation, culture and characterization of hESCs was first reported by Thomson and colleagues in 1998. In contrast to mESCs, hESCs resemble murine epiblast cells and are dependent on fibroblast growth factor (FGF) (Nichols and Smith 2009; Thomson et al. 1998).

Due to the reported differences between mouse and human ESCs, they were classified into two categories, namely, 'naive' or 'primed', related to the state of pluripotency. ESCs from mice, which are derived from the ICM, form dome-shaped colonies, and are responsive to LIF and capable of contributing to chimaeras when injected into other embryos, are classified as naive, whereas human ESCs, which form flat colonies, resemble epiblast cells, and are responsive to bFGF, are called primed. Interestingly, it has been demonstrated that both naïve and primed ECSs can be established in the mouse and that it is possible to promote a switch from one type to the other by changing culture conditions (Tosolini and Jouneau 2015). Until recently, reports have indicated that only naive cells could generate chimeric offspring (Nichols and Smith 2009; Rossant 2008). The dynamics of pluripotency regulation, however, has been shown a lot more plastic, at least in the murine model, in which stem cells derived from epiblast in postimplatation stage (EpiSCs) efficiently form chimeras in gastrulation-stage embryos, colonizing somatic and germ cell lineages. The inability of some types of stem cells to form or not chimeras is, therefore, better explained by their compatibility between environment and developmental stage more than capacity of in vivo differentiation (Huang et al. 2012).

The derivation of ESCs from domestic animals is highly desirable since it would greatly contribute to the development of a myriad of therapeutic and translational protocols. For decades, studies reported by various groups showed hurdles and promise in the attempts to maintain ESCs from domestic species in culture. However, consistency and reproducibility have remained lacking in the maintenance of the pluripotent state in vitro, the expression of pluripotency markers and even chimaera generation, probably resulting from the inability to understand the pathways maintaining pluripotency, to identify whether the ESCs are naive or primed, or even to identify further possible pluripotency-related states until now. The cell lines established so far are, therefore, referred to as ESC-like cells (Brevini et al. 2008; Nowak-Imialek et al. 2011).

Despite the hurdles described above, great progress has been recently reported. In mice, Yang et al. were able to modulate key developmental pathways in ES and iPS cells in order to obtain self-renewing stem cell lines with the expanded potential (EPSCs) for all blastocyst cell lineages, revealing possible important insights on the generation of these cells from other mammalian species (Yang et al. 2017). Importantly, in cattle, Bogliotti et al. reported that embryonic cells were able to be long term cultivated, maintained pluripotent characteristics in vitro, and also produced blastocysts when used as donor nuclei through the technique of core transfer or cloning. This finding is mainly due to the establishment of culture conditions conducive to maintenance of pluripotency, with supplementation with fibroblast basic factor (FGF2) and canonical Wnt-b-catenin signaling pathway inhibitor. Undoubtedly, this study may serve as a basis for the advancement of both further therapeutic progress, not achieved until now; and improvement of livestock (Bogliotti et al. 2018; Goszczynski et al. 2018).

New promise from pluripotent cells: Induced pluripotent stem cells (iPSCs) in domestic animals

Takahashi and Yamanaka, in 2006, and then several other groups achieved a significant advance in understanding the acquisition of the pluripotent state when they reported the in vitro reprogramming of mouse and human fibroblasts into pluripotent cells similar to ESCs via the forced expression of a combination of key stem cell specific transcription factors – originally Oct4, Sox2, Klf4 and c-Myc (OSKM), but also others such as Lin-28, Nanog and TCL-1A. The resultant cells, referred to as induced pluripotent stem cells (iPSCs) were characterized as being pluripotent according to the same pluripotency tests as used for ESCs: the formation of embryonic bodies, in vitro cell differentiation, the formation of teratomas in vivo and the capacity of forming viable embryonic chimaeras (Takahashi et al. 2007; Takahashi and Yamanaka 2006; Wernig et al. 2007; Picanço-Castro et al. 2011).

The generation of human and murine iPSCs became a true "game changer" in the field of stem cells and regenerative medicine, and indeed, a major achievement for veterinary medicine was the generation of pluripotent cells from other animals seen in the light of that "true" ESCs cannot be efficiently produced or maintained in vitro in these species as previously discussed (Nowak-Imialek et al. 2011; Muñoz et al. 2008).

In contrast to ESCs, iPSCs have already been produced in several animal species by using various methodologies to express the exogenous factors in the reprogrammed cells, including viral vectors (retrovirus, adenovirus and Sendai virus), nonviral vectors (episomal and minicircle vectors), and the piggyBac and Sleeping Beauty transposons. Species in which iPSCs have been reported include sheep (Li et al. 2011; Bao et al. 2011), goats (Song et al. 2013), horses (Nagy et al. 2011; Whitworth et al. 2014), cattle (Cao et al. 2012; Sumer et al. 2011), dogs (Goncalves et al. 2017; Koh and Piedrahita 2015; Nishimura et al. 2017) and felids (Verma et al. 2013; Verma et al. 2012).

The number of reports in each species, however, is still not high. For example, one study has derived iPSCs from endangered felids (Verma et al. 2012) and none from domestic cats until now, highlighting that, while the principal pluripotency mechanisms in mammals may follow similar patterns, certain particularities of each species can hampers its generation.

Although iPSCs generated from domestic animals are reportedly more robust than ESCs, much work remains to be ensure reproducibility and consistency. For example, the derivation of canine iPSCs (ciPSCs) seems to require co-culture with feeder cells, and supplementation with bFGF, LIF or both. Chemical inhibitors supplementation was also reported to be necessary for maintaining their undifferentiated status, however, no chimeric offspring has been reported to date (Koh et al. 2011; Luo et al. 2011a). Also, iPSCs derived from other species such as equine, swine and bovine have already been reported generated from different reprogramming conditions: different supplementation, with either 4 (Oct4, Sox2, Klf4 and c-Myc, OSKM) or 6 reprogramming factors - OSKM plus Nanog and Lin28 (OSKMNL), and most importantly, most of them did not show robust evidence, if any, of exogenous vector expression silencing, even when considered naïve-like and were able to contribute to embryonic and fetal tissues (Whitworth et al. 2014; Cao et al. 2012; Goncalves et al. 2017; Koh and Piedrahita 2015; Luo et al. 2011b; Baird et al. 2015; Shimada et al. 2009; Canizo et al. 2018; Fujishiro et al. 2013).

In brief, while the generation of iPSCs from domestic animals has been reported and is extremely promising for veterinary and translational medicine, the exact conditions needed for reprogram somatic cells from each species and to maintain a pluripotent state are far from being fully deciphered.

Stem cells in reproductive medicine: Where do we stand and where can we go?

The majority of studies concerning the use of stem cells in reproductive medicine have been carried out in animals, not as patients but as models for human conditions (reviewed in Vassena et al., 2015). MSCs have been reported as auxiliary treatments for reproductive disorders such as endometriosis and other conditions related to endometrium regeneration (Du and Taylor 2009; Vassena et al. 2015). IPSCs, however, hold great promise because they might enable the understanding of disease mechanisms and drug discovery in a similar way to that assumed for ESCs, with the advantage of enabling autologous transplant (Singh et al. 2015) and avoiding ethical conflicts.

Several studies have been performed in both humans and animals aiming to induce the differentiation of multipotent cells, ESCs or iPSCs into germ cells capable of producing gametes, which are the most specialized cells in an organism and essential to the continuation and evolution of the species (Neupane et al. 2008; Hübner et al. 2003; Nayernia et al. 2006; Clark et al. 2004). Primordial germ-like cells (PGCLs) generated by the induction of swine, probably multipotent cells from skin, showed the expression of germline markers (Vasa, Dazl, Stella) and meiosis markers (synaptonemal complex proteins), and morphological analysis showed similarity to oocytes (Dyce et al. 2006, 2011; Linher et al. 2009); however, no offspring was reported.

Protocols for PGC generation by using ESCs or iPSCs showed development into initial gametes, oocytes and spermatogonia expressing *VASA* and *DAZL* in PGCs induced with retinoic acid, BMP4 or even further supplementation with follicular fluid, cytokines or germ cell extracts (Panula et al. 2010; Castrillon et al. 2000; Kee et al. 2009; Park et al. 2009).

The generation of germ cells from somatic cells is still a rare and complex process, in which the similarities between in vitro induction and the in vivo process are not clear (Pelosi et al. 2011). Interestingly, some of these induced cells seems to lack specific imprinting in e.g. the *Igf2r* and *H19* genes, which is characteristic of germinative cells during migration prior to gamete development (Geijsen et al. 2004). Other studies, however, have identified mistakes during methylation remodelling of DNA that lead to the incomplete reprogramming of in vitro-derived male germ cells (Nayernia et al. 2006).

A milestone in the field, however, was recently reported in 2011 by Hayashi and colleagues when they described the generation of functional PGCLs from ESCs and iPSCs after pre-induction into epiblast-like cells (EpiLCs) in mice; these cells are capable of undergoing normal spermatogenesis or oogenesis and of giving rise to normal offspring (Hayashi et al. 2012; Hayashi et al. 2011). In vivo stages comprised of the need to transplant these cells into gonads, however, were necessary and certainly contributed to the success of offspring generation.

In 2016, the same group reported the in vitro reconstitution of the entirety of the female germ line, trough in vitro differentiation of PGCLs into primary oocytes, which required co-culture with gonadal somatic cells (Hikabe et al. 2016).

In domestic animals, the production of PGCLs from pluripotent cells may remain restricted due to the low efficiency of induced reprogramming into pluripotency, as well as the lack of knowledge regarding the real pluripotent status of iPSCs cells. Therefore, studies should be continued to clarify the molecular mechanisms involved in nuclear reprogramming.

Another topic that must not be forgotten when reviewing the possible applications of stem cells in reproductive medicine is the investigation of spermatogonial stem cells (SSCs). These cells are adult stem cells classified as unipotent (de Barros et al. 2012) that are responsible for promoting the maintenance of spermatogenesis through self-renewal and differentiation for continuous production of spermatozoa (Aponte 2015).

Brinstey and Avarbok (1994) first reported the transplantation of SSCs in mice and since then, a series of other studies on the restoration of fertility and the preservation of endangered species were envisioned and contributed to the investigation of the developmental mechanisms and function of germ stem cells (de Barros et al. 2012; Harkey et al. 2013; Tiptanavattana et al. 2013; Brinster and Avarbock 1994).

SSC transplantation in canines and cats was first achieved by Dobrinski et al. (1999) and Kim et al. (2008), respectively. Dobrinski (1999) observed that the more phylogenetically distant the donor species is from the receptor species, the lower is the differentiation capacity of the cells in the receptor and therefore the capacity to produce spermatozoa (Aponte 2015; Dobrinski et al. 1999; Kim et al. 2008; Travis et al. 2009). Travis et al. (2009) reported that in cats, the ectopic xenografting of 'donor' feline testicular tissue into a 'recipient' immunodeficient mouse is a promising tool to preserve the male genome from genetically valuable felids.

Transplantation of SSCs is important in the context of regenerative and translational medicine, especially when considering the possibilities of propagating male genetic material for research, better understanding of the biology of spermatogenesis, endangered species conservation, as well as offering new strategies for the treatment of infertility (Brinster 2002; Brinster and Zimmermann 1994).

Prospects and conclusion

This review presents an overview of the concepts, prospects and hurdles related to the derivation and use of different types of stem cells in domestic animals. Fig. 1 summarizes possible applications in both in vivo and in vitro models. However, stem cell research still lacks regulation and reproducibility, and the generation of pluripotent in animals other than humans

and mice doubtless presents a new route full of possibilities and hopes for a new era in the fields of veterinary reproductive and regenerative medicine, including, for example, the conservation of rare breeds and species and even the production of viable gametes from PGCLs. These technologies can also provide consistently replaceable stocks of experimental material for examining specific biological and developmental processes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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